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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,399	09/25/2003	Linda Pilarski	A894635US	1833

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,399	PILARSKI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-28 and 49-105* is/are pending in the application.

4a) Of the above claim(s) *24-26, 51-87, 91-105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23,27,49,50 and 88-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *12 July 2007*.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *notice of comply*.

Response to Argument and Amendment

The Amendment filed on 5/7/2007 in response to the previous Non-Final Office Action (11/6/2006) is acknowledged and has been entered.

Claims 1-20, 22, 29-48, and 106-107 have been cancelled. Claims 21, 23-28, 49-105 are pending. Claims 24-26, 51-87, 91-105 have been withdrawn previously for non-elected invention. Claims 21, 49, and 88 are amended to add SEQ ID NO: 4, 6, and 8 in the claims. However, The sequences in the newly amended claims are not originally elected HAS1Va of SEQ ID NO: 3 (a DNA sequence) as filed on 4/7/2004. Since applicant has received an action on the merits for the originally presented invention that a method of detecting expression of HAS1Va isoenzyme (SEQ ID NO: 3) comprising a step using primers of SEQ ID NO: 9 and 10, the expression of other HAS1 variants and protein of HAS1Va isoenzyme are not examined at this time. During a telephone conversation with Graig Sherburne on July 12, 2007, applicant decides to withdraw the SEQ ID NO: 6 and 8 from consideration under 37 CFR 1.142(b), as being drawn to a non-elected invention. Thus, claims 21, 23, 27, 28, 49, 50, and 88-90 drawn to a method of detecting HAS1Va isoenzyme, determining the likelihood of poor clinical outcome (claims 49, 50) and monitoring malignant cells (claims 88-90) to the extent of SEQ ID NO: 3 encoding HAS1Va isoenzyme protein of SEQ ID NO: 4 are under the consideration.

The following office action contains NEW GROUNDS of rejection.

Sequence Requirement

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Specifically, SEQ ID No(s) is required for Brief Description of the Drawing for Fig 5 and 18. If these sequences are found in the sequence listing filed 10/15/2003, Applicants need only insert the appropriate SEQ ID Nos. However, if these sequences are not part of the listing filed 10/15/2003, then Applicants need to comply with the sequence rules. Applicant is reminded to check the entire disclosure to ensure that the application is in sequence compliance (see attached PTO 90L for the details).

Rejections/Objections Withdrawn

1. The Objection of drawing (figure 9) is withdrawn in view of the submission of new drawing.

2. The rejection of claims 21, 23, 27, 49-50, and 88-90 under 35 U.S.C. 112, second paragraph, as being indefiniteness is withdrawn in view of amendment to the claims by adding the SEQ ID Nos. However, the amended claims are objected to as being drawn to a method of detecting a protein by oligoprimers DNA (see detail below).

3. The rejection of claims 49-50 and 88-89 under 35 U.S.C. 102(a) as being anticipated by Calabro et al., (Blood, vol 100, page 2578-2585, Oct, 2002, provided in previous office action) is withdrawn in view of amendment to the claims by adding the SEQ ID Nos.

Rejection Maintained and Response to Arguments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 88 and 90 remain rejected under 35 U.S.C. 102(a) as being anticipated by Adamia et al., (Seminars in Oncology, Vol 30, page 165-168, April 2003, provided in previously office action) as stated below:

> Adamia et al., disclose a method of monitoring malignant cells of Waldenstrom's Macroglomulemia (WM) patients by detecting aberrant expression of HAS1 isozyme variants in bone marrow cells from WM patients. Adamia et al., disclose that overexpression of HAS isozyme variants contribute to malignant growth and spread in WM patients and also disclose expression patterns of the HAS gene promote migration of the WM cells in the patients (page 165, abstract, page 166 table 1).

Applicant although amended claims by adding SEQ ID Nos (protein sequence) the reference still anticipates claimed invention because the claims do not recite the specific primers used for the detection

and the method in the reference seem using the same method step for the same patient population. The HAS1Va detected in the method of Adamia et al., appear to be the same HAS1Va having DNA sequence of SEQ ID NO: 3 encoding the protein of SEQ ID NO: 4 in the claimed method. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

The response filed 5/7/2007 has been carefully considered but is deemed not to be persuasive. The response states that Adamia et al., represents the applicants own authored publication and disclosure, which was made available to the public less than one year of effective filing date of current publication. This rejection is not statutory bar under 35 USC 102 (b) or 103. In response to this argument, The statue above clearly states: the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country. MPEP 2132 further defines term by others in 35 U.S.C. 102(a) as:

III. "BY OTHERS"

"Others" Means Any Combination of Authors or Inventors Different Than the Inventive Entity

The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use. Any other interpretation of 35 U.S.C. 102(a) "would negate the one year [grace] period afforded under § 102(b)." In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

The inventive entity of this application is different from the combined authors in the publication. Therefore the reference meet the requirement under 35 U.S.C. 102(a). Thus, applicant's argument has not been found persuasive, and the rejection is maintained.

The following is a New Ground of rejection-based on the amendment to the claims

Specification

Specification is objected to for typographical error as "fig 19" on page 29. The instant specification does not provide fig 19 and last figure in the drawings is figure 18. Appropriate correction is required.

Objection of claims

1. The amended claims 21, 23, 27, 28, 49, 50, 88-90 are objected to as being drawn to a method reciting nonelected invention. Applicants have elected SEQ ID NO: 3, the DNA sequence for HAS1 variant A (HAS1Va) for examination in response to the restriction requirement filed on 4/7/2004. Although the Office has noted that the HAS1Va variant protein (SEQ ID NO: 4) is encoded by a nucleotide sequence of SEQ ID NO: 3, currently amended claims do not recite elected SEQ ID NO: 3 in the claimed method. Since applicant has already elected DNA of HAS1Va (SEQ ID NO: 3) encoding the protein of SEQ ID NO: 4 for examination and claimed method is drawn to PCR detection of nucleotides, the Office suggests amending the claims including detecting HAS1Va nucleotide shown by DNA sequence, for example SEQ ID NO: 3 in the method.

2. Claims 21, 23, 27, 28, 49, 50, and 88-90 are objected to because of the following informalities: The specification provides definition and description of HAS family protein as Hyalurona synthase isoenzymes comprising HAS1Va (page 5-7), line 23-28). However, the abbreviation HAS1 or HAS1Va etc. should be spelled out when first used in the claims. Appropriate correction is required.

***Rejection under 35 USC § 112, first paragraph*-Scope of enablement:**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 23, and 27 remain and 49, 50, 88-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for detecting gene expression of elected HAS1Va, the DNA shown by nucleotide sequence of SEQ ID NO: 3 encoding the protein having amino acid sequence SEQ ID NO: 4, by PCR with oligonucleotide primers, SEQ ID NO: 9 and SEQ ID NO: 10, does not reasonably provide enablement for the method of detecting other HAS1 isoenzyme variants by using this set of primers or other method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The method objective of claims is detecting HAS1 isoenzyme variants by PCR using oligonucleotide primers of SEQ ID NO: 9 and SEQ IDNO: 10 or a method of monitoring a malignant cell in comparing detecting HAS isoenzyme having protein SEQ ID NO: 4 encoding by a DNA of SEQ ID NO: 3. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. Thus, it would be expected that one of skill in the art would be able to detect all the HAS1 isoenzyme variants by using the claimed method including the primer set of SEQ ID NO: 9 and 10.

The specification discloses HAS1 isoenzyme variants HAS1Va, HAS1Vb, and HAS1Vc having a DNA sequence of SEQ ID NO: 3, 5, and 7. The specification discloses a method of On-chip PCR using oligonucleotide primers of SEQ ID NO: 9 and SEQ ID NO: 10 for detecting the gene expression of HAS1Va shown by SEQ ID NO: 3 (page 51-52). The specification, in example 1, discloses a method of detecting HAS1 variants by RT-PCR, but no primers are disclosed. HAS1 isoenzyme variants,

understood by one skilled in the art, comprise a large numbers of spliced variants alternated from wild type of HAS1 gene, which include mutated, deleted, or inserted forms of the gene products, in which the nucleotide sequences could have been already defined or have not been defined yet in the art. These variants would be structural and sequence different gene products, in which the sequence may be altered at any place of the gene or gene product. More important, one skilled in the art has recognized that not all the variants of HAS1 express to make proteins because the short lifetime of the transcript in the normal and pathological condition including Multiple myeloma (MM, Adamia et al., Blood, vol 105, page 4836 col 1, 2005). Using designed set of primers (SEQ ID NO: 9 and SEQ ID NO: 10) according to HAS1Va DNA sequence may only detect HAS1Va having a sequence of SEQ ID NO: 3 or any deletion or insertion of nucleotides between the binding sites of the primers in the SEQ ID NO: 3 with a confirmation of sequencing the detected fragment. Detection by PCR of other insertion, deletion, or mutation at any other place of HAS1Va or any other HAS1 containing no matched sequence with the primers is not enabled and must be undue experimentation with the new primer set. This is the case here, for example, the specification discloses three variants of HAS1V, HAS1Va (SEQ IDNO: 3), HAS1Vb (SEQ IDNO: 5), and HAS1Vc (SEQ ID NO:7). The primers (SEQ ID NO: 9 and SEQ ID NO: 10) will detect a fragment of HAS1Va (SEQ ID NO: 3) between nucleotide 876-966, which is not even present in the HAS1Vc (SEQ ID NO: 7, see sequence search provided in previous office action). Accordingly, any other variants of HAS1 having nucleotide changes beyond than the nucleotide sequence between 876-966 would not be detectable with the set of the primers (SEQ ID NO: 9 and SEQ ID NO: 10). Applicants have not provided any teaching on any other specific variant of HAS1 being detected by the method using primers of SEQ ID NO: 9 and SEQ ID NO: 10 or using any other method. In addition, the claims 49, 50, and 88-90 are amended to drawn to a method of monitoring a disease by detecting HAS isoenzyme variant having SEQ ID NO: 4, 6, and 8. As discussed above, the specification only describes a method of measuring the HAS1 isoenzymes by PCR using the primer set of SEQ ID NO: 9 and 10. The primers are designed for detecting DNA of SEQ ID NO: 3 encoding HAS1Va of SEQ ID NO: 4, not for other variants.

Moreover, one skilled in the art has recognized that using one set primers for detecting one of the isoenzyme may not be useful for the other isoenzyme detection. For example, Calabro et al., (Blood, vol

100, page 2578-2585, Oct, 2002, provided in previous office action) teach a method of determining malignancy and monitoring malignant cells in multiple myeloma (MM) patient by detecting HAS1, 2 and 3 gene product, specifically mRNA expression by a set of primers listed on table 1, line 1 for HAS1 (page 2579). However, the primer set disclosed by Calabro et al., does not detect any HAS1 variants defined by the SEQ ID Nos listed in the claims because the forward primer having nucleotide sequence 5'-GTGAGTGGCTGTACAACGCG-3' located at position 1021-1040 of SEQ ID NO: 3 and reverse primer is located nowhere of the SEQ ID NO: 3 encoding HAS1 isoenzymes of SEQ ID NO: 4. Thus. In absence of sequence homology or identity between the primers to the detected template, one skilled in the art clearly know that they could not use claimed method to monitor the disease by using claimed method. The specification does not disclose any other enabled method for detecting all the variants for monitoring the disease.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to the method of detecting expression of HAS1 isoenzyme variants other than HAS1Va with primers SEQ ID NO: 9 and SEQ ID NO: 10, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention. If applicant has any objective evidence contrary to the rejection, applicant is invited to submit it to the Office for consideration.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

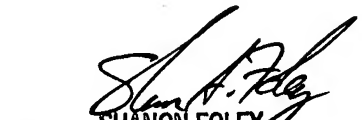
Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY



SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10672399	Applicant(s) Pilarski et al	
	Examiner Lei Yao	Art Unit 1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Need SEQ ID NOs for brief description of the drawing , Fig 5 and 18.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
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